A COMPARISON OF THE PHARMACOKINETICS OF BACAMPICILLIN, AMPICILLIN, AMOXICILLIN, AND CYCLACILLIN: ORAL ADMINISTRATION IN INFANTS AND CHILDREN*

GEORGE M. MCCRACKEN, JR., M.D.

Professor of Pediatrics
University of Texas Health Science Center
Southwestern Medical School
Dallas, Texas

RECENT introduction of the semisynthetic penicillins, bacampicillin, amoxicillin, and cyclacillin, has provided a larger array of ampicillin-like drugs for management of otitis media and acute urinary tract infections in pediatric patients. Pharmacokinetic studies in adults have shown that peak concentrations of bacampicillin and amoxicillin are greater than those of ampicillin after equivalent doses.[1-4] Bacampicillin, a prodrug of ampicillin, is more completely and more rapidly absorbed from the gastrointestinal tract than ampicillin and leads to peak serum ampicillin levels approximately three times the levels obtained after administration of equivalent amounts of ampicillin. Amoxicillin produces blood levels that are lower than bacampicillin but approximately twice those of ampicillin. Although the half lives of the three drugs are similar, the area under the curve values and eight-hour urinary recovery values for bacampicillin and amoxicillin exceed those of ampicillin.[5-6]

The present studies were conducted to provide the pharmacokinetic data for bacampicillin, amoxicillin, and cyclacillin in pediatric patients. Three independent, crossover comparisons were made over a period of two years to evaluate the comparative pharmacokinetics of bacampicillin and ampicillin, amoxicillin and ampicillin, and cyclacillin and amoxicillin.[7-9] These trials were conducted to formulate proper dosage schedules for these drugs in infants and children and to measure serum concentrations, urinary levels, and the role of feeding status on drug absorption.

*Presented as part of a *Symposium on Recent Developments in Oral Antibiotic Therapy: Bacampicillin Update* held by the Section on Pediatrics and the Section on Medicine of the New York Academy of Medicine, December 19, 1982. This symposium was supported by a grant from Roerig, division of Pfizer Pharmaceuticals.

MATERIALS AND METHODS

The studies were conducted in the outpatient clinic of Children's Medical Center, Dallas, Texas. Infants and young children with acute otitis media or skin infections were eligible for inclusion in the investigations. House officers in the clinic were responsible for clinical diagnosis and management. Written parental consent was obtained for each patient prior to enrollment in the studies. A total of 72 infants and children from three to 59 months of age were studied. Their weights ranged from 4.4 to 21 kg and their heights ranged from 60 to 112 cm. Each child was included in one of three drug comparisons.

Bacampicillin vs. ampicillin. Each child included in this study received either bacampicillin hydrochloride (125 mg/5 ml) or ampicillin trihydrate (250 mg/5 ml) oral suspension in four divided doses.[7] Of the 20 children given the bacampicillin oral suspension, seven received the microcapsule formulation currently in use and the remainder received an investigational formulation subsequently discontinued. The data presented herein are based on the group using the microcapsule form. Most children received both bacampicillin and ampicillin in a crossover design, with a four- to five-day interval between studies. Drugs were administered while the children were fasting. Blood samples were obtained immediately before and at one-half, one, two, four, and six hours after drug dosing.

Amoxicillin vs. ampicillin. Each child included in this study received either ampicillin trihydrate or amoxicillin trihydrate oral suspension (125 or 250 mg/5 ml) administered in three or four divided doses.[8] Most children were studied on two separate occasions: once while fasting and once when drug was administered with 4 oz of milk or formula Similac® or Enfamil®). Thirteen children received amoxicillin alone; 11 children received both drugs in crossover fashion, with a six- to seven-day interval between studies. Blood samples were obtained immediately before and at one-half, one, two, four, and six hours after drug dosing.

Cyclacillin vs. amoxicillin. Each child included in this study received either cyclacillin or amoxicillin trihydrate oral suspension (125 or 250 mg/5 ml) administered four or three times daily, respectively, for 10 days.[9] Most children were studied on two separate occasions: once while fasting and once when drug was administered with 4 oz of milk or formula (Similac® or Enfamil®). Fifteen children received cyclacillin alone; 12 children received both drugs in crossover fashion, with a four-

to five-day interval between studies. Blood samples were obtained immediately before and at one-quarter, one-half, three-quarters, one, three, and six hours after dosing.

None of the children in any of the investigations received other medications before or during the studies. The same research nurse administered the drugs to all children. None of the samples obtained from any patient prior to treatment contained detectable antimicrobial activity. All blood samples were obtained using a heparin-lock and wing-tip needle inserted into a peripheral vein.

Assay. Concentrations of the antibiotics in body fluids were assayed according to a micro-method utilizing *Sarcina lutea* (ATCC 9341; American Type Culture Collection, Rockville, Md.) as the test organism. Test and reference samples were diluted identically either in serum (for measurement of serum concentrations) or in phosphate-buffered saline, pH 6.0 (for measurement of urine levels).

Pharmacokinetic analysis. The equation for the regression line of the log serum concentrations of antibiotic against time was calculated by the method of least mean squares. The serum half life was determined by dividing $\log_{10}2$ by the slope of the line. The area under the serum concentration curve, expressed as micrograms per milliliter per hour, was formulated by successive trapezoidal approximation.[10]

Statistical analysis. Data were analyzed by Bartlett's test for equal variance.[11] The two groups were compared by the Mann Whitney U test when significant differences between values were found. Differences in values were considered significant if the p value was ≤ 0.05.

RESULTS

One hundred forty pharmacokinetic studies were performed in 75 infants and children. Serum concentrations, half lives, and area under the curve values for equivalent doses of bacampicillin, ampicillin, amoxicillin, and cyclacillin are shown in the table.

Bacampicillin vs. ampicillin. A mean peak drug concentration in serum of 14.4 μg/ml was observed one hour after ingestion of 27.3 mg of bacampicillin/kg body weight (equivalent to 19 mg/kg of ampicillin). The half life in serum was 1.8 hours. A peak mean drug concentration in serum of 5.0 μg/ml was noted one hour after ingestion of 25 mg/kg of ampicillin; the half life in serum was 1.1 hours.

CONCENTRATION IN SERUM, HALF-LIFE, AND AREA UNDER THE CURVE (AUC) OF EQUIVALENT DOSAGES OF BACAMPICILLIN, AMPICILLIN, AMOXICILLIN, AND CYCLACILLIN IN INFANTS AND CHILDREN

Drug (mg/kg)	*Feeding status*	*Mean concentrations of drugs in serum (μg/ml)*								*Serum half life (hr)*	*AUC (μg/ml/hr)*
		0.25 hr	*0.5 hr*	*0.75 hr*	*1 hr*	*2 hr*	*3 hr*	*4 hr*	*6 hr*		
Bacampicillin (27.8 mg/kg)	Fasting	—	8.4	—	14.4	6.7	—	1.4	0.44	1.8	29
Ampicillin	Fasting	—	3.4	—	5.0	2.9	—	0.7	0.2	1.1	12
(25 mg/kg)	Fed	—	2.8	—	4.1	2.9	—	1.0	0.3	1.1	12
Amoxicillin	Fasting	—	5.8	—	8.9	6.3	—	1.7	0.6	1.2	24
(25 mg/kg)	Fed	—	4.3	—	7.9	6.3	—	2.2	0.7	1.2	24
Cyclacillin	Fasting	11.1	25.6	21.3	19.0	—	1.52	—	0.14	0.7	42
(25 mg/kg)	Fed	13.7	27.0	25.6	19.7	—	2.1	—	0.25	0.79	44

AUC = Area under the curve

The pharmacokinetic values after a dose of 27.8 mg/kg of bacampicillin were compared with those after a dose of 25 mg/kg of ampicillin in the 21 infants who received both drugs in crossover fashion. Although the dosage of bacampicillin used in this study was 25% smaller than that of ampicillin, drug concentrations in serum after administration of bacampicillin were consistently higher at all intervals than those after ampicillin. Peak drug concentrations in serum one hour after administration of bacampicillin were approximately three times larger than those at one hour after a dose of ampicillin trihydrate (14.4 μg/ml vs. 4.8 μg/ml; $p = 0.001$).

A single urine specimen was obtained from each patient at a random time during the six-hour study period. Mean concentrations of drug in urine obtained up to three hours after the dose were 1,815 μg/ml (range, 370−4,400 μg/ml) in patients who received bacampicillin and 949 μg/ml (range, 155−2,100 μg/ml) in patients who received ampicillin. Children taking bacampicillin had a mean urinary concentration of 1,176 μg/ml (range, 250−3100 μg/ml) three to six hours after dosing, compared to 379 μg/ml (range, 35−650 μg/ml) in children receiving ampicillin.

Amoxicillin vs. ampicillin. Mean peak drug concentrations in serum of 5.4 and 8.9 μg/ml in fasting and of 3.2 and 7.9 μg/ml in nonfasting infants were noted at one hour after 15 mg/kg and 25 mg/kg amoxicillin doses, respectively (see table). Differences in six-hour serum values between fasting and nonfasting patients were of borderline significance ($p = 0.07$) in the group receiving 15 mg/kg doses. This trend was not observed at any time period in the group receiving 25 mg/kg amoxicillin. Serum half lives and area under the curve values were similar for fasting and nonfasting patients in both groups. The drug was present in the serum of all patients at six hours at mean concentrations ranging from 0.14 to 3.3 μg/ml in the 15 mg/kg amoxicillin group, and from 1.01 to 1.17 μg/ml in the 25 mg/kg amoxicillin group.

Mean peak serum concentrations of 4.1 μg/ml in nonfasting and of 5.0 μg/ml in fasting infants were noted one hour after ingestion of 25 mg/kg ampicillin (see table). Differences in serum concentrations between the two groups were not statistically significant at any time interval. The drug was present in the serum of all patients at six hours at mean concentrations ranging from 0.2 to 0.3 μg/ml.

Comparison of the pharmacokinetic values of ampicillin and amoxicillin revealed significantly larger ($p = 0.01$) serum concentrations of amoxicillin (25 mg/kg) in fasting patients two hours after dosing than in either

fasting or fed patients receiving ampicillin. Differences in serum concentrations at four and six hours in both fasting and fed patients were of borderline statistical significance. The serum concentrations of amoxicillin (25 mg/kg) were consistently larger than those of ampicillin in both fasting and fed patients at all time intervals. These differences were of borderline significance one and two hours after dosing and reached statistical significance at four and six hours.

The half life times for amoxicillin and ampicillin were similar (ranging from 1.1 to 1.2 hours), except that a serum half life of 1.8 hours was observed in nonfasting patients receiving 15 mg/kg doses of amoxicillin. The area under the curve values for 15 mg/kg amoxicillin were comparable to those of 25 mg/kg ampicillin (ranging from 12 to 16 μg/ml/hr), whereas the area under the curve values for 25 mg/kg amoxicillin were approximately twice as large (24 μg/ml/hr).

A single urine specimen was obtained from each patient at a random time during the six hour study period. Concentrations of amoxicillin in urine were independent of feeding status and ranged from 84 to 3,900 μg/ml. Mean concentrations of 15 mg/kg amoxicillin in urine obtained up to two hours after drug dosing were 858 μg/ml (range, 123−1,460 μg/ml), and 1,378 μg/ml (range, 351−1,860 μg/ml) after two to four hours. Mean values of 1,374, 1,458, and 989 μg/ml were noted at zero to two, two to four, and four to six hours, respectively, after dosing with 25 mg/kg amoxicillin.

Cyclacillin vs. amoxicillin. Mean peak drug concentrations in serum of 25 μg/ml in fasting infants and 27 μg/ml in nonfasting infants were observed 30 minutes after administration of 25 mg/kg cyclacillin (see table). Fasting patients receiving 15 mg/kg cyclacillin showed mean peak serum concentrations of 15.6 μg/ml 30 minutes after dosing. There were no statistically significant differences in serum concentrations between fasting and nonfasting patients receiving the 25 mg/kg formulation at any time interval. The peak concentrations obtained at 30 minutes with both the 15 mg/kg and 25 mg/kg dosage forms declined rapidly after the first hour. By six hours, drug could not be detected in the serum of any patient receiving the 15 mg/kg form and in 35% of patients receiving the 25 mg/kg form.

A pharmacokinetic comparison of cyclacillin (15 mg/kg) and amoxicillin (15 mg/kg) was conducted in 12 patients receiving both drugs in crossover fashion. Peak serum concentrations were achieved more rapidly with cyclacillin (30 minutes) than with amoxicillin (60 minutes); the mean peak serum concentration of cyclacillin (15.6 μg/ml) was significantly

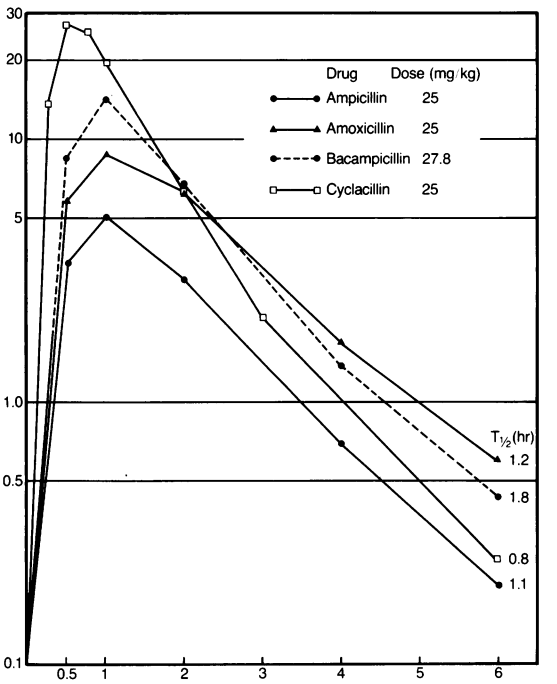

Fig. 1. Serum concentration — time curves.

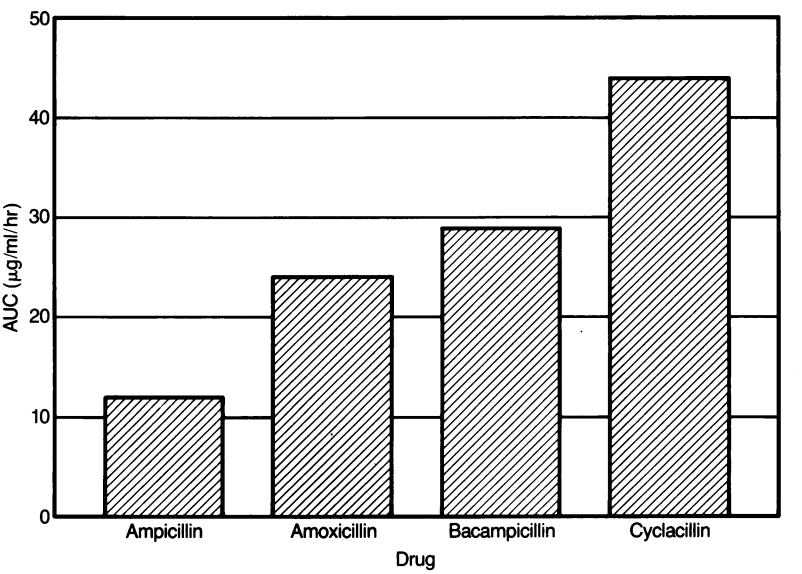

Fig. 2. Area under the curve values after equivalent doses of 25 mg/kg.

larger than that of amoxicillin (7.3 μg/ml). Although the serum concentrations of cyclacillin were significantly larger than those of amoxicillin during the first 45 minutes, the reverse was true at all subsequent time intervals. The cumulative six hour area under the curve values were similar for both cyclacillin and amoxicillin (19 and 18 μg/ml/hr respectively), whereas the mean half life times were significantly larger for amoxicillin (mean, 1.2 hours) than for cyclacillin (mean, 0.59 hour).

A single urine specimen was obtained from each patient at a random time during the six hour study period. Concentrations of cyclacillin in urine were independent of feeding status and ranged from 18.5 to 6,250 μg/ml. No samples were obtained during the first two hours of the study period. The average concentration in urine obtained from two to four hours after dosing with 25 mg/kg cyclacillin was 1,066 μg/ml (range, 18.5−4,450 μg/ml) and 1,384 μg/ml (range, 34−6,250 μg/ml) four to six hours after dosing.

The serum concentration time curves and area under the curve values for all four drugs are represented in Figures 1 and 2.

Discussion

These pharmacokinetic studies reveal that the semisynthetic penicillins are, in general, rapidly and well absorbed, but dissimilarities in the pharmacokinetic profiles of these drugs are apparent. The relevance of these findings to clinical efficacy is uncertain.

Bacampicillin, ampicillin, and amoxicillin achieve peak serum concentrations one hour after dosing, whereas cyclacillin reaches its peak serum concentration within 30 minutes. The rapid absorption associated with administration of cyclacillin theoretically may be offset by the considerably shorter serum half life. Cyclacillin was the only drug of the four studied whose antimicrobial activity could not be detected in any serum sample at six hours and whose rapid decline in serum concentrations began within one hour after dosing. The minimal inhibitory and bactericidal concentration of cyclacillin of commonly encountered pathogens (*Streptococcus pneumoniae* and *Hemophilus influenzae*) are larger than those for the other drugs. The importance of this finding to clinical use remains to be defined.

Peak serum concentrations of bacampicillin at one hour were almost triple those of ampicillin and double those of amoxicillin, and its serum half life of 1.8 hours exceeded that of both ampicillin (1.1 hours) and

amoxicillin (1.2 hours). The larger bioavailability of bacampicillin after oral administration to infants and children may be advantageous for oral therapy of skeletal infections or pneumonia caused by susceptible strains of *H. influenzae* or *Enterobacteriaceae*. Additional information is required before the role of bacampicillin for such therapy can be properly determined.

REFERENCES

1. Rozencweig, M., Staquet, M., and Klastersky, J.: Antibacterial activity and pharmacokinetics of bacampicillin and ampicillin. *Clin. Pharmacol. Ther. 19:*592–97, 1976.
2. Giebel, W., Schönleber, K.-H., Breuninger, H., and Ullmann, U.: A comparison of the pharmacokinetics in serum and nasal secretions after oral bacampicillin and ampicillin. *Scand. J. Infect. Dis.* (Suppl.) *14:*285–87, 1978.
3. Gordon, R. C., Regamey, C., and Kirby, W. M. M.: Comparative clinical pharmacology of amoxicillin and ampicillin administered orally. *Antimicrob. Agents Chemother. 1:*504–07, 1972.
4. Neu, H. C. and Winshell, E. B.: Pharmacological studies of 6 [D (−) α-amino-*P*-hydroxyphenylacetamido] penicillanic acid in humans. *Antimicrob. Agents Chemother. 10:*423–26, 1970.
5. Spyker, D. A., Rugloski, R. J., Vann, R. L., and O'Brien, W. M.: Pharmacokinetics of amoxicillin: dose dependence after intravenous, oral, and intramuscular administration. *Antimicrob. Agents Chemother. 11:*132–41, 1977.
6. Verbist, L.: Triple crossover study on absorption and excretion of ampicillin, talampicillin, and amoxicillin. *Antimicrob. Agents Chemother. 10:*173–75, 1976.
7. Ginsburg, C. M., McCracken, G. H., Jr., Clahsen, J., and Zweighaft, T.: Comparative pharmacokinetics of bacampicillin and ampicillin suspensions in infants and children. *Rev. Infect. Dis. 3:*117–20, 1981.
8. Ginsburg, C. M., McCracken, G. H., Thomas, M. L., and Clahsen, J.: Comparative pharmacokinetics of amoxicillin and ampicillin in infants and children. *Pediatrics 64:*627–31, 1979.
9. Ginsburg, C. M., McCracken, G. H., Jr., Zweighaft, T. C., and Clahsen, J. C.: Comparative pharmacokinetics of cyclacillin and amoxicillin in infants and children. *Antimicrob. Agents Chemother. 19:*1086–88, 1981.
10. Ritschel, W. A., editor: *Handbook of Basic Pharmacokinetics*. Hamilton, Ill., Drug Intelligence Publications, 1976, pp. 235–43.
11. Zar, G., editor: *Biostatistical Statistical Analysis*. Englewood Cliffs, N.J., Prentice-Hall, 1974.